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MATERNAL-FETAL MEDICINE

First pregnancy risk factors and future gestational diabetes mellitus

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Abstract

Purpose Gestational diabetes mellitus (GDM) affect about 17% of all pregnancies and is associated with significant short- and long-term health consequences for the mother and her offspring. Early diagnosis and prompt interventions may reduce these adverse outcomes. We aimed to identify first pregnancy characteristics as risk factors for GDM in subsequent pregnancy.

Materials and methods A population-based nested case–control study was conducted in a large tertiary hospital. The study population included all women with two singleton consecutive pregnancies and deliveries, without GDM in the first pregnancy. Characteristics and complications of the first pregnancy were compared among cases and controls. A multivariable logistic regression model was used to study the association between pregnancy complications (in the first pregnancy) and GDM in the subsequent pregnancy, while adjusting for confounding variables.

Results A total of 38,750 women were included in the study, of them 1.9% ($n=728$) had GDM in their second pregnancy. Mothers with GDM in their second pregnancy were more likely to have the following first pregnancy complications: hypertensive disorders, perinatal mortality, maternal obesity and fetal macrosomia. Results remained significant after adjustment for maternal age and inter-pregnancy interval. Having either one of the complications increased the risk for GDM by 2.33 (adjusted OR = 2.33; 95% CI 1.93–2.82) while a combination of two complications increased GDM risk by 5.38 (adjusted OR = 5.38; 95% CI 2.85–10.17).

Conclusions First pregnancy without GDM complicated by hypertensive disorders, perinatal mortality, maternal obesity and fetal macrosomia was associated with an increased risk for GDM in the subsequent pregnancy. Women with these complications may benefit from early detection of GDM in their subsequent pregnancy.

Keywords Gestational diabetes mellitus · GDM · Pregnancy complications

Abbreviation

GDM Gestational diabetes mellitus

Introduction

The global prevalence of gestational diabetes mellitus (GDM) has increased over the past decades and is estimated to affect 17% of pregnancies and about 21.4 million live births yearly [1]. GDM management includes lifestyle changes, nutritional counseling and, if needed, oral or injectable drugs [2, 3]. Risk factors for GDM include GDM at previous pregnancy, advanced maternal age, family history of diabetes, macrosomia and obesity [4, 5].

Even under tight glycemic monitoring, women with GDM are at a higher risk for long-term metabolic diseases [6, 7]. The offspring of GDM mothers are prone to neonatal short-term morbidities [8] and a wide range of long-term complications [9–17]. In a randomized controlled trial, the treatment of mild GDM with dietary advice, blood glucose monitoring and insulin therapy as needed resulted in a reduced incidence of macrosomia in the intervention group, but there was no effect on BMI at the age of 4–5 years old [18]. These findings regarding the long-term health effects on both the mother and her offspring may be explained, at least partly, by the fact that GDM screening is performed only at the 24th week of pregnancy, possibly after some damage has already occurred [19, 20].

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Several tools are suggested for early detection of GDM including the following: First trimester measurement of insulin resistance combined with anthropometric measurements [21], a combination of biochemical markers (maternal fetuin-A, N-terminal proatrial natriuretic peptide (pro-ANP), high-sensitivity C-reactive protein (hs-CRP), and fasting glucose levels at 11–14 gestation weeks [22]) and even proteomic tests in the first trimester [23]. These tests are expensive, not performed routinely, and are usually offered to women at risk for GDM. Detection of GDM earlier in pregnancy may improve maternal, perinatal and offspring health [19, 24].

Since early treatment may improve perinatal and possibly maternal and offspring long-term health, [19] and early detection tests are not usually available, it is important to identify women at risk for GDM who may benefit from these early detection screening tests.

The aim of the current study was to identify risk factors in first pregnancy for GDM in the subsequent pregnancy.

Materials and methods

A retrospective population-based nested case-control study was conducted at the Soroka University Medical Center (SUMC) located in the Southern region of Israel. SUMC, the sole tertiary medical center in the region, serves a population of > 1 million residents and has the country`s largest birthing center with > 17,000 birth/year in recent years. The study included all women with two first singleton consecutive deliveries of first two consecutive pregnancies (with no pregnancies before the 1st or the 2nd pregnancies that ended in abortion), between the years 1991 and 2017. Only women with documented and accurate matching of parity and gravidity, and with full medical records on both pregnancies and deliveries, were included. To avoid over-diagnosis among women with previous pregnancy complications, women with insufficient prenatal care were excluded from the study. Gestational diabetes mellitus (GDM) was defined based on either one of the following ICD-9 codes: 648.01 or 648.81. Women with GDM in the first pregnancy were excluded as well as multiple gestations (in either pregnancy), women with pre-gestational diabetes diagnosed before either their first or second pregnancy and women with insufficient prenatal care in their second pregnancy (to minimize the possibility of misclassification of the cases). Low birthweight was defined as birthweight < 2500 gr, preterm delivery: delivery < 37 gestational weeks, macrosomia: birthweight > 4000 gr, hypertensive disorders: elevated blood pressure (systolic ≥ 140 or diastolic ≥ 90 mm Hg, within the first 20 weeks of pregnancy (chronic hypertension) or after 20 weeks of gestation with previously normal blood pressures (gestational hypertension), GDM: 2 or more pathological results in oral glucose tolerance test and obesity was defined as BMI > 30

Statistical analyses

Cases were defined as women with GDM in their second pregnancy and were compared to the controls, defined as women without GDM in their second pregnancy. Characteristics and complications of the first pregnancy were compared between cases and controls, using chi-square test and student *t* tests. First pregnancy characteristics and complications that were significantly different between cases and controls were tested in the multivariable analysis. Multivariable logistic regression models were used to study the association between first pregnancy complications and GDM in the subsequent pregnancy, while adjusting for maternal age and inter-pregnancy interval (IPI). IPI was calculated as the number of years between first delivery and best estimation of the first day of the last menstruation period of the second pregnancy, based on clinical evaluation and first trimester ultrasound measurements.

In addition to specific pregnancy complications, a combined adverse pregnancy score was created, which summed the number of first pregnancy complications which were associated with second pregnancy GDM (based on the first step analysis): macrosomia (birthweight > 4000 gr.), obesity (pre-pregnancy BMI > 30), pregnancy related hypertensive disorders (including the following ICD codes: 642.41; 642.51; 642.42; 642.52; 642.61; 642.62), and perinatal mortality. Scoring ranged between 0 = no complications; 1 = one complication; 2 = two complications. Two dummy variables were created to compare the risk in women with one vs. no complications and women with two vs. no complications. Women with no first pregnancy complications served as the reference group.

Ethical approval

The study protocol was approved by the SUMC IRB and informed consent was exempt.

Results

Approximately, 83,000 women delivered during the study period. Complete records for all deliveries were available for 53,593 women, 43,572 had verified documentation on first and second consecutive pregnancies and deliveries (Fig. 1). Out of them, 4822 had GDM in the first pregnancy or no complete follow-up, yielding a total of 38,750 women which were included in the study (77,500 deliveries) and 1.9% of second pregnancies were diagnosed with GDM ($n = 728$, i.e., Cases.

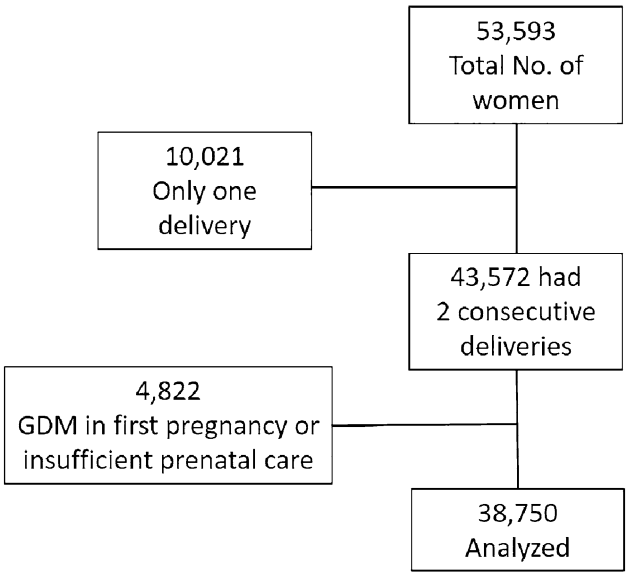

Fig. 1 Participant flowchart

Cases, as compared to controls, were older in their first pregnancy and were more likely to have the following complications in their first pregnancy (Table 1): preterm delivery (13.3% vs. 8.4%; OR = 1.68; 95% CI 1.35–2.09, $p < 0.01$), hypertensive disorders (13.9% vs. 6.5%; OR = 2.32; 95% CI 1.87–2.88, $p < 0.001$), perinatal mortality (3.7% vs. 1.2%; OR = 3.05; 95% CI; 2.06–4.53, $p < 0.001$), cesarean delivery (23.2% vs. 12.9%; OR = 2.05; 95% CI 1.72–2.44, $p < 0.001$) and delivered a macrosomic newborn (4.4% vs. 2.0%; OR = 2.29; 95% CI 1.60–3.29). The inter-pregnancy interval was longer among cases than controls (846 ± 798 and 575 ± 562 days, respectively, $p < 0.001$).

Table 2 presents the odds ratios and adjusted odds ratios for the association between first pregnancy characteristics and GDM. The multivariable models adjusted for maternal age and inter-pregnancy interval. Maternal obesity, delivery of a macrosomic newborn, pregnancy-related hypertensive disorders and fetal mortality were all independently associated with an increased risk for GDM in subsequent pregnancy.

Table 2 Odds ratios and adjusted odds ratios for the association between first pregnancy characteristics and GDM

Variable	Unadjusted odds ratio; 95% CI	Adjusted odds ratio; 95% CI[a]	*p*
Hypertensive disorders	2.32; 1.87–2.88	2:33; 1.80–2.77	< 0.001
Perinatal death	3.05; 2.06–4.53	3.60; 2.39–5.41	< 0.001
Maternal obesity	3.92; 1.57–9.75	3.00; 1.19–7.57	< 0.001
Macrosomia	2.29; 1.60–3.29	2.04; 1.42–2.97	< 0.001

[a]Adjusted for maternal age and inter-pregnancy interval

In the combined score, which included obesity, macrosomia, pregnancy-related hypertensive disorder and perinatal mortality, there were 34,950 (90.2%) women without first pregnancy complications; 3,680 (9.5%) women with one complication in first pregnancy and 120 (0.3%) women with two complications in first pregnancy. The incidence of second pregnancy GDM by first pregnancy diagnosis as well as the combined score is presented in Fig. 2.

In the multivariable model, women who scored 1 or 2 in the combined adverse pregnancy score were compared to women scoring zero. While adjusting maternal age and inter-pregnancy interval, having a history of either one of the first pregnancy complications, was independently associated with an increased risk for GDM (adjusted OR for a single risk factor = 2.33; 95% CI 1.93–2.82, $p < 0.001$), and the risk was higher when having two complication (adjusted OR = 5.38; 2.85–10.17, $p < 0.001$).

Table 1 First pregnancy characteristics by cases and controls

	Cases (GDM in 2nd pregnancy) *n* = 728 (1.9%)	Controls (no GDM in 2nd pregnancy) *n* = 38,022 (98.1%)	OR; 95% CI	*p* value
Maternal age (mean ± SD)	25.10 ± 4.2	23.26 ± 4.0		< 0.001
Birthweight (mean ± SD)	3093 ± 663	3050 ± 523		0.09
Gestational age (mean ± SD)	38.5 ± 2.8	39.0 ± 2.1		< 0.001
Cesarean delivery, *n* (%)	169 (23.2)	4889 (12.9)	2.05; 1.72–2.44	< 0.001
Preterm delivery (< 37 gestational weeks), *n* (%)	97 (13.3)	3191 (8.4)	1.68; 1.35–2.09	< 0.001
Low birthweight (< 2,500 gr.), *n* (%)	95 (13.0)	4205 (11.1)	1.21; 0.97–1.50	0.09
Macrosomia, *n* (%)	32 (4.4)	747 (2.0)	2.29; 1.60–3.29	< 0.001
Obesity, *n* (%)	5 (0.7)	67 (0.2)	3.92; 1.57–9.75	0.011
Perinatal mortality, *n* (%)	27 (3.7)	474 (1.2)	3.05; 2.06–4.53	< 0.001
Hypertensive disorders, *n* (%)	101 (13.9)	2467 (6.5)	2.32; 1.87–2.88	< 0.001
Placental abruption, *n* (%)	4 (0.5)	218 (0.6)	0.96; 0.36–2.58	1.00
Inter pregnancy interval, days (mean ± SD)	846 ± 798	575 ± 562		< 0.001

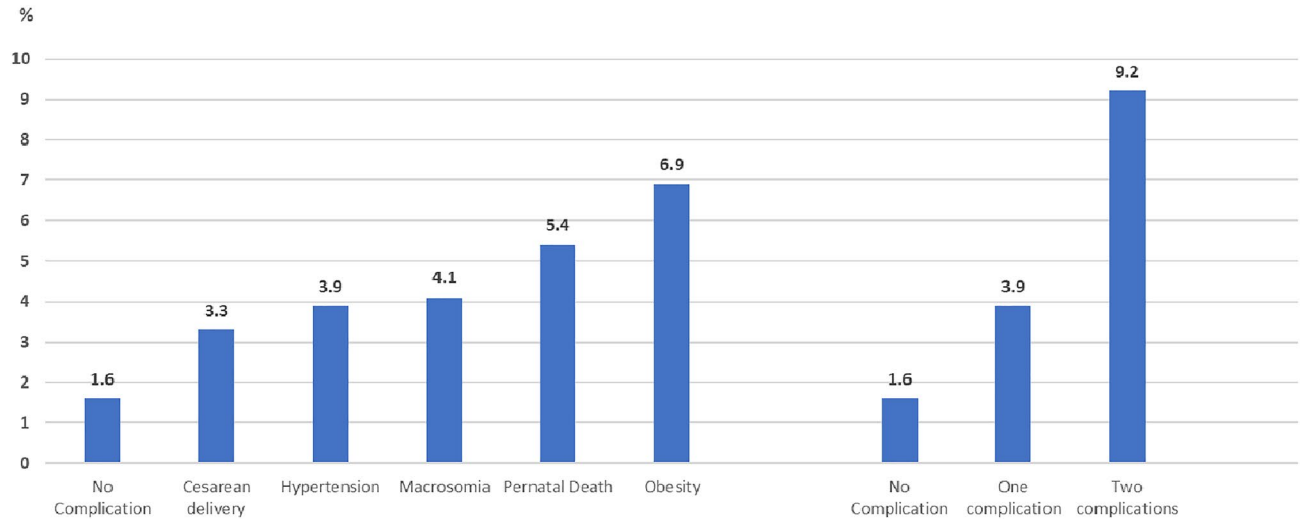

Fig. 2 Risk for GDM in subsequent pregnancy by first pregnancy complications

Discussion

In the current study, women without GDM in first pregnancy but with other complications were at increased risk for developing GDM in their second pregnancy. These complications were: cesarean delivery, delivery of a macrosomic newborn, pregnancy-related hypertensive disorders, preterm delivery and perinatal mortality.

Various underlying basic pathologies in the first pregnancy may lead to GDM in the subsequent one. As women age, glucose tolerance deteriorates and the incidence of GDM increases [25, 26]. Thus, women with GDM in second pregnancy may have had borderline or undetected mild dysglycemia in previous pregnancy, which resulted in macrosomia or lead to a caesarean section.

Emerging data point toward common pathophysiological mechanisms in preeclampsia and GDM [27]. Metformin, an anti-diabetic agent, has been found to effectively treat preeclampsia [28–31]. A common mechanism may explain the association between a history of preeclampsia and GDM risk in the subsequent pregnancy. 5′ adenosine monophosphate-activated protein kinase (AMPK), a serine/threonine protein kinase, may be a crucial element in the basic pathophysiology of hypertensive disorders of pregnancy, preterm birth (PTB) and GDM.

AMPK is a key modulator of energy at the cellular level as well as whole-body energy homeostasis, mainly under stressful conditions. During pregnancy, AMPK is essential for the proper placental function, nutrient transportation and maternal and fetal energy homeostasis [32, 33]. Proper regulation of AMPK is vital for normal placental and embryonic development, and its dysregulation may lead to placental insufficiency, intrauterine growth restriction and preeclampsia [34–37]. Progesterone is crucial for uterine resilience and the prevention of premature labor. AMPK was also found to play a key role in progesterone receptor function [38].

Besides the role of AMPK in preeclampsia and PTB etiology, it has a critical role in proper glucose metabolism [39], and AMPK function was found to be modulated by the antidiabetic drug Metformin [40–43].

Since many prenatal complications tent to reoccur, findings regarding AMPK function may, at least partly, explain the association between perinatal complications in the first pregnancy and GDM in the subsequent one. Other mechanisms may also be involved, and further studies are recommended to fully understand the association between the different pregnancy complications and future GDM.

Among the strengths of the current study is the large population-based study in a single tertiary hospital; therefore, full data regarding both pregnancies per women were available. However, due to the retrospective study design, data regarding other potential confounding variables was unavailable, including exact maternal BMI and environmental exposures. Additionally, this study design can point to associations only and not to causality.

GDM, in most cases, is diagnosed at 24 gestational weeks using the oral glucose challenge test, when adverse metabolic imprints may have already affected the placenta, the mother and the fetus. Early GDM screening may be recommended for women with previous pregnancy complications such as pregnancy related hypertensive disorders, preterm delivery, fetal macrosomia or perinatal mortality, and even more so, for women with more than one of these complications. With the increasing incidence of GDM, its early diagnosis will be relevant to larger populations and will possibly prevent perinatal complications and improve both the mother's and the offspring's short- and long-term health.

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Declarations

Conflicts of interests None of the authors have any commercial association or other conflicts of interest regarding the manuscript.

Consent to participate Not applicable.

Consent for publication Not applicable.

Ethics approval The study protocol was approved by the Institutional IRB and informed consent was exempt.

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